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A non- synonymous polymorphism in galactose mutarotase (*GALM*) is associated with serotonin transporter binding potential in the human thalamus: Results of a genome-wide association study

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Positron emission tomography (PET) imaging using the tracer [^{11}C]DASB is a sensitive and noninvasive technique for measuring brain serotonin transporter (5-HTT) levels in vivo[1] . Previously, Cannon et al. found that 5-HTT levels were increased in thalamus, striatum, insular and cingulate cortices in unmedicated, depressed subjects with major depressive disorder[2] or bipolar disorder[3]. To explore this potential biomarker for mood disorders, we undertook a proof-of-principle genome-wide association study.

5-HTT levels, measured as [^{11}C]DASB binding potential (BP_{ND}), were assessed in six brain regions-of-interest (ROIs). Healthy (n=22) and unmedicated participants diagnosed with bipolar disorder (n=16) or major depressive disorder (n=17), aged 18 to 48 years (Mean ± SD, 34 ± 9 yr) underwent PET scanning with [^{11}C]DASB. Subject ascertainment, PET scanning, and analysis were described previously[2-3]. DNA was extracted from peripheral blood and genotyped on the Illumina Human-1 SNP array. Genotypes were called with

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BeadStudio v3.0. Data were filtered for minor allele frequencies < 1%, missing genotype rates > 8%, Hardy-Weinberg Equilibrium p-values <0.05, gender mismatch, and hidden relatedness. A total of 93,427 SNPs passed all quality control filters for all of the ROIs tested. Association analysis was performed by linear regression in PLINK[4] (v1.02), with 3 covariates to control for ancestry. Genomic Control lambda values were all <1.05, indicating good control of confounding factors

Overall, 5 SNPs representing 5 different genes met our FDR<0.1 criterion for being declared of interest: rs6741892 in *GALM*, rs390704 near *FRY*, rs7161217 near *TTLL5*, rs583241 near *CPLX4*, and rs7095106 near *CASC2*. The strongest association was between thalamic [^{11}C]DASB-BP$_{ND}$ and a coding SNP in the gene *GALM* (rs6741892, $p=4.67\times10^{-8}$; FDR=0.004). This result meets the threshold of genome-wide significance under typical frequentist assumptions, but not if corrected for 6 ROIs. rs6741892 accounted for about 50% of the variance in [^{11}C]DASB-BP$_{ND}$ in thalamus. Carriers of the "TT" genotype showed the highest [^{11}C]DASB-BP$_{ND}$.

Since the T-allele frequency differed by self-reported ancestry (10/13 in African-Americans, 3/13 in whites, and 0/7 in Hispanics), we also performed the analysis within each ancestry group, then combined the p-values by meta-analysis (META 5.3, http://userpage.fuberlin.de/~health/meta_e.htm), with similar results. We further confirmed this finding in a voxel-based analysis (Fig 1).

Nominally-significant associations were also observed between rs6741892 and [^{11}C]DASB-BP$_{ND}$ in dorsal cingulate cortex (DCC; $p=4.03\times10^{-2}$) and insula ($p=1.14\times10^{-3}$). No SNPs near the gene encoding the 5-HTT (SLC6A4) showed significant association in this sample, consistent with one prior study[5], but we may have missed a true association due to lack of power. Rs6741892 was also individually genotyped using a modification of the 5′ nuclease (Taqman) assay, with similar results.

Consistent with our prior findings[2,3], we found a significant main effect of diagnosis on [^{11}C]DASB-BP$_{ND}$ measured in thalamus ($F(2, 52)=7.07$, $p<0.002$) due to significantly higher thalamic [^{11}C]DASB-BP$_{ND}$ in participants with mood disorders. However, the overall association results were not dependent on diagnosis: rs6741892 was also associated with [^{11}C]DASB-BP$_{ND}$ in healthy participants.

Supportive evidence of association with rs6741892 was obtained from an independent replication sample of 51 European-ancestry subjects (16 females aged 43±20 yr, 35 males aged 34±18 yr) ascertained in Denmark, using TaqMan. Imaging and analysis were as described[6]. Significant associations were observed between rs6741892 and [^{11}C]DASB-BP$_{ND}$ in DCC ($p=3.5\times10^{-3}$) and insula ($p=4.9\times10^{-3}$), but not in thalamus, although [^{11}C]DASB-BP$_{ND}$ is highly correlated across subcortical structures[7]. Combined analysis with META 5.3 supported association between rs6741892 and [^{11}C]DASB-BP$_{ND}$ in all 3 regions of interest (DCC, $p=9.18\times10^{-4}$; insula, $p=3.25\times10^{-5}$; and thalamus, $p=4.6\times10^{-6}$).

GALM encodes galactose mutarotase, which catalyzes the conversion of beta-D-galactose to alpha-D-galactose[8], important in carbohydrate metabolism and the production of complex oligosaccharides. Galactose mutarotase might affect regional neurophysiology, leading to

local increases in serotonin release and in membrane trafficking of 5-HTT[9], thereby increasing [^{11}C]DASB-BP_{ND}. Galactose mutarotase may also play a role in N-glycosylation, which is important for surface expression of 5-HTT[10].

To our knowledge, this is the first genome-wide association study of brain 5-HTT. These preliminary results suggest that neuroimaging phenotypes could represent informative targets for a GWAS, even in relatively small samples. Further studies are needed to confirm these findings and determine the underlying biological mechanisms.

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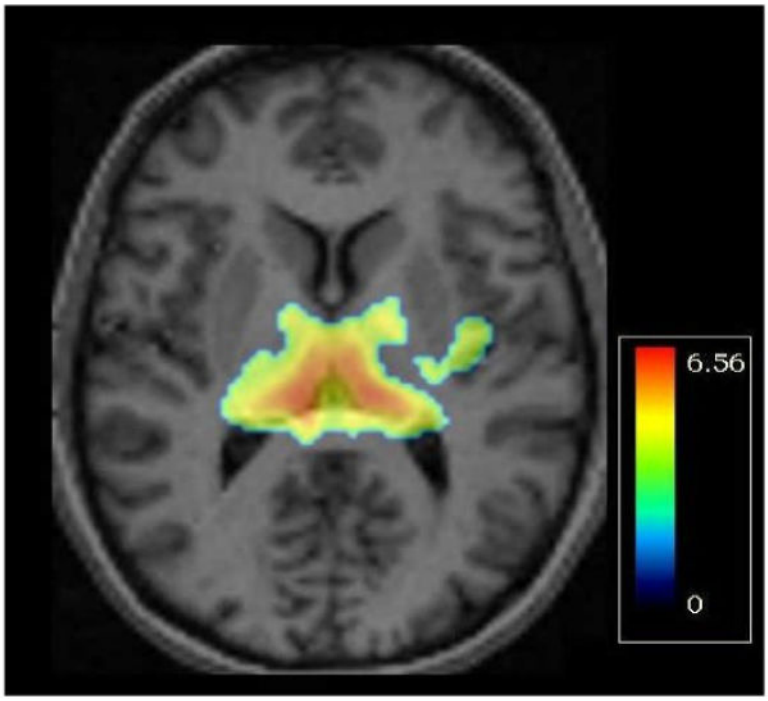

Figure 1.

Map of t-values from voxel-wise analysis of rs6741892, overlaid on a sample axial MRI slice at the level of the medial thalamus (z=6 mm). Bilaterally, T-allele carriers (n=13) have greater serotonin-transporter binding potential than AA homozygotes (n=42). The color bar indicates the range of t-values displayed (max t = 6.56, df=53, $p=2.3 \times 10^{-8}$).